IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Molecular Loop Biosciences, Inc., Plaintiff, v. Illumina, Inc. and Verinata Health, Inc., Defendants.	Civil Action No. _____ **JURY TRIAL DEMANDED**

COMPLAINT

Plaintiff Molecular Loop Biosciences, Inc. ("Molecular Loop"), for its Complaint against Defendants Illumina, Inc. ("Illumina") and Verinata Health, Inc. ("VHI") (collectively "Defendants"), hereby alleges as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 11,041,852 ("the '852 Patent"), 11,768,200 ("the '200 Patent"), and 11,840,730 ("the '730 Patent") (collectively the "Patents-in-Suit"), arising under the Patent Laws of the United States, 35 U.S.C. §§ 271 *et seq*.

THE PARTIES

2. Plaintiff Molecular Loop is a Delaware corporation with its principal place of business at 300 Tradecenter Drive #5400, Woburn, Massachusetts 01801. Molecular Loop is a pioneering company that focuses on developing sequencing technologies, including technology for next generation sequencing ("NGS"). Molecular Loop's technology is a fundamental part of what makes NGS more scalable, efficient, and practical. Molecular Loop's technology has various applications, including in reproductive testing, oncology testing, and other genetic applications.

3. Defendant Illumina is a company organized and existing under the laws of the State of Delaware, with its principal place of business at 5200 Illumina Way, San Diego, California, 92122. (Ex. 4 at 1 (Illumina Inc. Form 10-Q, May 3, 2024).) Illumina has appointed The Corporation Trust Company, Corporation Trust Center 1209 Orange Street, Wilmington, Delaware 19801, as its agent for service of process. (Ex. 5 at 1 (State of Delaware Entity Status for Illumina, Inc.).)

4. Defendant VHI is a company organized and existing under the laws of the state of Delaware, with its principal place of business at 5200 Illumina Way, San Diego, California 92122. VHI has appointed The Corporation Trust Company, Corporation Trust Center 1209 Orange Street, Wilmington, Delaware 19801, as its agent for service of process. (Ex. 6 at 1 (State of Delaware Entity Status for Verinata Health, Inc.).) VHI is a wholly owned subsidiary of Illumina. (*See, e.g.*, Ex. 7 at 106 (Illumina Inc. Form 10-K, February 16, 2024).)

5. Defendants, themselves and/or through their subsidiaries and affiliates, make, use, and commercialize genetic tests marketed under the tradename "VeriSeq" that utilize NGS and include DNA library preparation kits that incorporate identifier sequences and data analysis methods that reduce errors after amplification and sequencing.

6. Defendants, themselves and/or through their subsidiaries and affiliates, make, use, and commercialize non-invasive prenatal tests marketed under the tradename "Verifi" that utilize NGS and include DNA library preparation kits that incorporate identifier sequences and data analysis methods that reduce errors after amplification and sequencing.

7. Defendants, themselves and/or through their subsidiaries and affiliates, make, use, and commercialize oncology tests marketed under the tradename "TruSight" that utilize next-

generation sequencing and include DNA library preparation kits that incorporate identifier sequences and data analysis methods that reduce errors after amplification and sequencing.

8. Defendants, themselves and/or through their subsidiaries and affiliates, make, use and commercialize sequencing products, including products marketed under the names "Illumina DNA/RNA UD Indexes, Tagmentation," "IDT for Illumina DNA/RNA UD Indexes, Tagmentation," "IDT for Illumina Nextera UD Indexes," and "AmpliSeq UD Indexes for Illumina," for use in NGS applications to reduce errors after amplification and sequencing.

9. Defendants, themselves and/or through their subsidiaries and affiliates, offer NGS services to other labs, which includes DNA library preparation methods that incorporate identifier sequences and data analysis methods that reduce errors after amplification and sequencing.

10. Defendants offer and market products under the tradenames Verifi; VeriSeq; TruSight; Illumina DNA/RNA UD Indexes, Tagmentation; IDT for Illumina DNA/RNA UD Indexes, Tagmentation; IDT for Illumina Nextera UD Indexes; and AmpliSeq UD Indexes for Illumina throughout the United States, including through its website: https://www.illumina.com/products.html. (*See generally* Ex. 8 (https://www.illumina.com/products/by-brand/trusight-oncology.html), Ex. 9 (https://www.illumina.com/clinical/illumina_clinical_laboratory/verifi-prenatal-tests.html), Ex. 10 (https://www.illumina.com/products/by-type/ivd-products/veriseq-nipt.html).)

JURISDICTION AND VENUE

11. Molecular Loop incorporates by reference paragraphs 1–10.

12. This action arises under the patent laws of the United States, including 35 U.S.C. §§ 271 *et seq*. The jurisdiction of this Court over the subject matter of this action is proper under 28 U.S.C. §§ 1331 and 1338(a).

13. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and (c), and 1400(b), because Illumina and VHI are entities organized under the laws of Delaware and reside in Delaware for purposes of venue under 28 U.S.C. § 1400(b). Defendants conduct business in Delaware, at least by offering for sale and selling products and services through their websites, which are accessible in Delaware. Defendants have also committed and continue to commit acts of infringement in this District.

14. This Court has personal jurisdiction over Defendants because Defendants conduct business in Delaware by at least offering for sale or selling products and services through Illumina's website, which is accessible in Delaware, and because infringement has occurred and continues to occur in Delaware.

15. Personal jurisdiction also exists over Illumina and VHI because they are entities organized under the laws of Delaware.

BACKGROUND OF THE INVENTIONS

16. The mission of Molecular Loop and its patented technology is to innovate the field of sequencing by improving efficiency and accuracy with technologies that are scalable and accessible to any laboratory. For example, through its novel techniques in targeted sequencing, Molecular Loop designed a SARS-CoV-2 NGS research panel for characterizing and monitoring the virus that caused the COVID-19 pandemic.

17. Prior to founding Molecular Loop, Dr. Greg Porreca was a co-founder and Chief Technology Officer of Good Start Genetics. Good Start Genetics, one of the first companies to launch NGS-based testing, provided accessible carrier screening and preimplantation embryo genetic testing to future parents using its scalable NGS platform, which allowed for a simpler workflow and affordable prices while maintaining quality results. Prior to founding Good Start,

Dr. Porreca earned his Ph.D. in genetics in the Church Lab at Harvard, where Dr. Porreca developed one of the first NGS platforms.

18. In NGS applications, multiple samples collected from different patients or sample types were pooled together to be sequenced at the same time in an effort to decrease costs and increase efficiency. This was known as multiplex sequencing.

19. Prior to the inventions of the Patents-in-Suit, errors were often introduced during NGS (for example during amplification and sequencing) and jeopardized the ability to accurately analyze the sequencing reads. For example, prior to Molecular Loop's inventions, template molecules collected from different samples could overlap on a substrate during solid phase amplification. This molecular overlap created incorrect molecules that could be further amplified and caused sequencing data to be assigned to the wrong sample. This type of error is illustrated in the Patents-in-Suit.

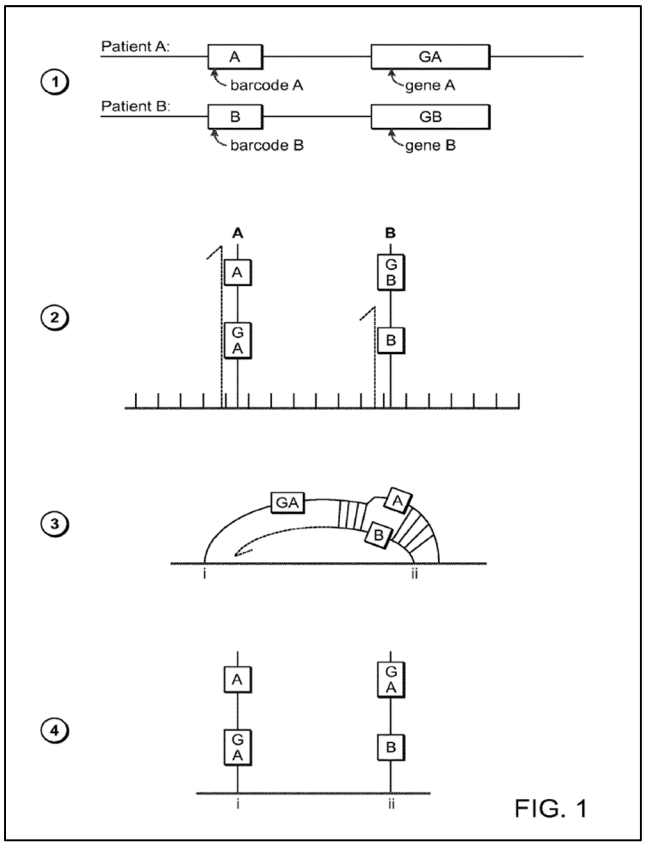
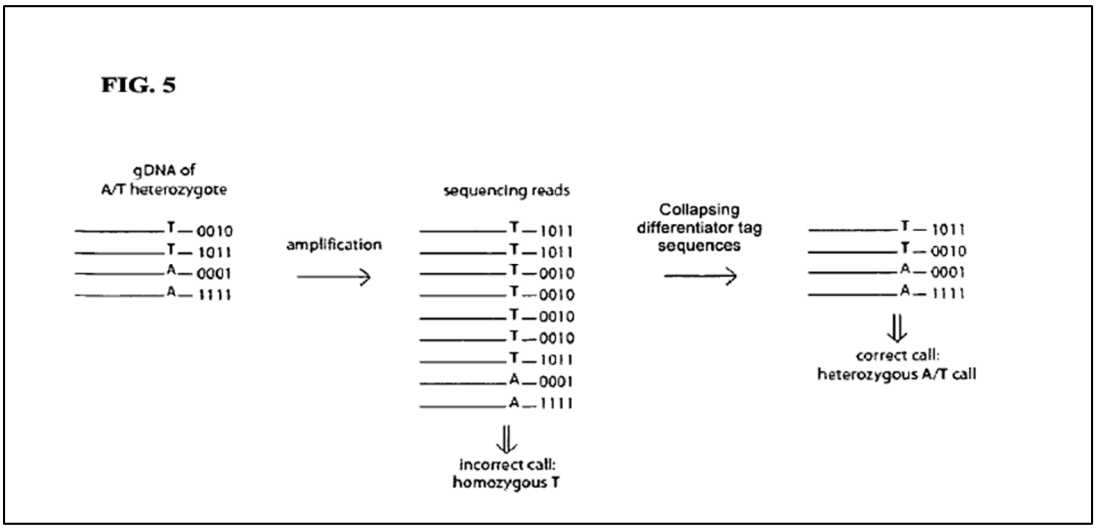


FIG. 1

'852 Patent at Fig. 1.

20. Prior to the inventions of the Patents-in-Suit, other errors could also arise during sequencing, such as incorrect addition of a base during amplification or sequencing, over-amplification of an individual starting molecule, or under-amplification of an individual starting molecule. For example, prior to Molecular Loop's inventions, data analysis methods were often unable to differentiate between multiple copies of a nucleic acid sequence that existed in a sample prior to amplification and multiple copies of a nucleic acid sequence that were generated during amplification of a single starting molecule containing the sequence. Errors could result from that difficulty, for example by causing an incorrect "homozygous" identification due to a significant mismatch in the comparison of one allele to another allele. Earlier sequencing technologies were often susceptible to such errors because they were unable to trace a particular amplicon back to a particular starting molecule.



'730 Patent at Fig. 5.

21. Errors arising during sequencing workflows could have drastic effects on the accuracy of downstream data analysis.

22. Prior to Molecular Loop's inventions, existing technologies were not sufficiently scalable, cost-effective, or accurate for genotyping samples efficiently, for example during multiplex sequencing when many patient samples are pooled together, due to errors introduced by existing sequencing workflows. Prior technologies thus could not accurately analyze large numbers of patient samples without implementing expensive and time-consuming workflows.

23. Dr. Porreca and his co-inventors recognized that by preparing nucleic acid samples with certain identifier sequences, downstream errors could be recognized and corrected during sequencing data analysis to increase accuracy. For example, by "tagging" starting molecules with certain identifiers corresponding to a given sample or molecule, amplicons could later be accurately traced back to the original sample or starting molecule, allowing for different sequences to be correctly demultiplexed, identified, and/or analyzed.

THE PATENTS-IN-SUIT

24. Molecular Loop incorporates by reference paragraphs 1-23.

25. The Patents-in-Suit are directed to, among other things, novel methods used in reducing bias and error in sequencing nucleic acids.

A. The '852 Patent

26. The '852 Patent, entitled "Methods for Maintaining the Integrity and Identification of a Nucleic Acid Template in a Multiplex Sequencing Reaction," was duly and legally issued by the United States Patent and Trademark Office on June 22, 2021. The inventors of the patent are Dr. Gregory Porreca, Dr. Mark Umbarger, and Dr. George Church, and the patent is assigned to Molecular Loop. A copy of the '852 Patent is attached hereto as Exhibit 1.

27. Molecular Loop is the exclusive owner of all rights, title, and interest in the '852 Patent, and has the right to bring this suit to recover damages for any current or past infringement of the '852 Patent. (*See* Ex. 11 ('852 Patent Assignment to Molecular Loop).)

28. The ’852 Patent claims an unconventional, non-routine method of incorporating identifier sequences to reduce error. For example, Claim 1 of the ’852 Patent recites:

> A method for reducing template cross-over error introduced during sequencing workflow, the method comprising the steps of
>
> incorporating at least two members of a plurality of identifier sequences into template nucleic acids obtained from at least two different samples, wherein said two members constitute a distinct pair associated with said template;
>
> combining said nucleic acid templates into a single sample;
>
> amplifying said nucleic acid templates on a surface of a flow cell thereby to form clusters, at least one of which comprises a chimeric sequence comprising a combination of identifier sequences that are different than any of said distinct pairs;
>
> sequencing amplicons obtained in said amplifying step; and
>
> discarding sequence reads obtained in said sequencing step that contain said combination of identifier sequences that are different than any of said distinct pairs, thereby to reduce cross-over error.

29. The ’852 Patent explains that, *inter alia*, the claimed inventions overcame problems in the field related to using single barcode sequences. For example, when only a single barcode is attached per template molecule, molecules may still be erroneously classified as high-quality sequences when they in fact contain incorrect sequence data. (*See* ’852 Patent at 5:18-6:52, Fig. 3.) When such molecules are formed in the early stages of amplification, later amplification cycles result in an entire cluster of its copies, leading to many molecules with incorrect sequences that are attributed to the wrong sample during sequencing. (*See* ’852 Patent at 6:35-53.)

30. By using at least a pair of identifier sequences, the ’852 Patent explains that new molecules that are formed from amplification errors (or distortion) will contain an incorrect pair of identifier sequences. (*See* ’852 Patent at 6:55-7:38, Fig. 3.) Downstream data analysis could recognize that the molecule contains an invalid identifier pair. (*See* ’852 Patent at 7:24-38.) Thus, reads for these molecules could be identified as error and discarded in data analysis.

31. The ’852 Patent illustrates the benefit of using a pair of identifiers by showing that molecules resulting from errors during amplification will contain an incorrect pair of identifiers, allowing recognition of these molecules later during data analysis.

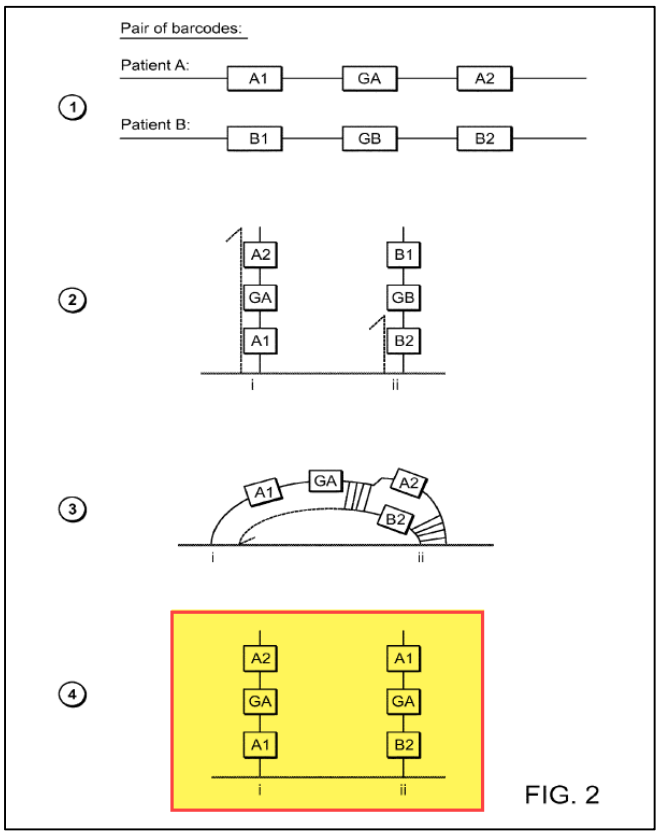


FIG. 2

’852 Patent at Fig. 2 (highlighting added).

32. The ’852 Patent teaches that one benefit of Molecular Loop’s inventions is realized by performance of the claimed method, including through integration of a pair of identifier sequences (e.g. barcode sequences) into each sample, such that each pair is attributed to a particular sample:

> The first and second barcode sequences are designed such that each pair of sequences is correlated to a particular sample, allowing samples to be distinguished and validated. Methods of designing sets of barcode sequences is shown for example in Brenner et al. (U.S. Pat. No. 6,235,475), the contents of which are incorporated by reference herein in their entirety. In certain embodiments, the barcode sequences range from about 2 nucleotides to about 50; and

> preferably from about 4 to about 20 nucleotides. Since the barcode sequence is sequenced along with the template nucleic acid or may be sequenced in a separate read, the oligonucleotide length should be of minimal length so as to permit the longest read from the template nucleic acid attached. Generally, the barcode sequences are spaced from the template nucleic acid molecule by at least one base. …
>
> Barcode sequence is integrated with template using methods known in the art. Barcode sequence is integrated with template using, for example, a ligase, a polymerase, Topo cloning (e.g., Invitrogen's topoisomerase vector cloning system using a topoisomerase enzyme), or chemical ligation or conjugation. The ligase may be any enzyme capable of ligating an oligonucleotide (RNA or DNA) to the template nucleic acid molecule. Suitable ligases include T4 DNA ligase and T4 RNA ligase (such ligases are available commercially, from New England Biolabs). Methods for using ligases are well known in the art. The polymerase may be any enzyme capable of adding nucleotides to the 3' and the 5' terminus of template nucleic acid molecules. Barcode sequence can be incorporated via a PCR reaction as part of the PCR primer.

'852 Patent at 9:14-28, 9:39-53.

33. The '852 Patent also teaches the immobilization of "capture oligonucleotides" to locations on the surface of a solid support structure, forming clusters. '852 Patent at 11:3-49, 11:64-12:22. Capture oligonucleotides can contain template specific portions that are complementary to a primer binding sequence found on a nucleic acid molecule (the "template molecule"). *Id.* Cluster formation aids in controlling the density of template molecules when amplified and can allow hybridization specificity or amplification of only certain oligonucleotide species:

> A uniform, homogeneously distributed lawn of immobilized oligonucleotides may be formed by coupling (grafting) a solution of oligonucleotide species onto the solid support. The solution can contain a homogenous population of oligonucleotides but will typically contain a mixture of different oligonucleotide species. . . . The density of the capture oligonucleotides can be controlled to give an optimum cluster density of 10^6 -10^9 clusters per cm^2 and optimum cluster brightness. The ratio of capture oligonucleotide species to the amplification oligonucleotide species can be any desired value

> including, but not limited to at least 1:100, 1:1000 or 1:100,000 depending on the desired cluster density and brightness. Similar densities or ratios of other molecular species can be used in embodiments where molecules other than nucleic acids are attached to a surface.
>
> In a particular embodiment, for each cluster of template molecules, a complementary copy of a single stranded polynucleotide template molecule is attached to the solid support by hybridization. Methods of hybridization for formation of stable duplexes between complementary sequences by way of Watson-Crick base-pairing are known in the art. The immobilized capture oligonucleotides can include a region of sequence that is complementary to a region or template specific portion of the single stranded template polynucleotide molecule. An extension reaction may then be carried out in which the capture sequence is extended by sequential addition of nucleotides to generate a complementary copy of the single stranded polynucleotide sequence attached to the solid support via the capture oligonucleotide. The single stranded polynucleotide sequence not immobilized to the support may be separated from the complementary sequence under denaturing conditions and removed, for example by washing.
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> …
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> In one aspect of the invention, one or more of the amplification primers can be modified to prevent hybridization of a region or template specific portion of the single stranded polynucleotide molecule. Alternatively or additionally, one or more of the amplification primers may be modified to prevent extension of the primer during one or more extension reactions, thus preventing copying of the hybridized templates. These modifications can be temporary or permanent.

'852 Patent at 11:64-12:40, 12:56-64; *see also id.* at 17:34-65.

B. <u>The '200 Patent</u>

34. The '200 Patent, entitled "Methods for Maintaining the Integrity and Identification of a Nucleic Acid Template in a Multiplex Sequencing Reaction," was duly and legally issued by the United States Patent and Trademark Office on September 26, 2023. The inventors of the patent of Dr. Gregory Porreca, Dr. Mark Umbarger, and Dr. George Church, and the patent is assigned to Molecular Loop. A copy of the '200 Patent is attached hereto as Exhibit 2.

35. Molecular Loop is the exclusive owner of all rights, title and interest in the '200 Patent, and has the right to bring this suit to recover damages for any current or past infringement of the '200 Patent. (*See* Ex. 12 ('200 Patent Assignment to Molecular Loop).)

36. The '200 Patent is a continuation of the '852 Patent. The '200 Patent claims an unconventional, non-routine method of incorporating identifier sequences into a sample with a nucleic acid analyte of interest to allow for future and correct identification of that analyte as belonging to the sample. For example, Claim 1 recites:

> A method for validating the sequence of a nucleic acid analyte of interest in a multiplex sequencing reaction, the method comprising:
>
> i) detecting the presence of two or more identifier sequences that are uniquely associated with the nucleic acid analyte of interest, wherein at least a first identifier sequence is incorporated into a 5' portion of the nucleic acid analyte of interest and wherein at least a second identifier sequence is incorporated into a 3' portion of the nucleic acid analyte of interest, and wherein the first and second identifier sequences have four or more nucleotides and are different;
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> ii) sequencing the first identifier sequence, the nucleic acid analyte of interest and the second identifier sequence; and
>
> iii) validating the sequence of the nucleic acid analyte of interest by analyzing both identifiers and excluding the sequences of those nucleic acid analytes of interest containing only one identifier or an incorrect pair of identifiers from sequence analysis of the multiplex sequencing reaction.

37. The '200 Patent explains that the set of identifiers incorporated into a given sample are correlated to that particular sample, which allows a sequence to be traced back to that sample during analysis. '200 Patent at 9:5-28. The '200 Patent also teaches amplification of nucleic acid molecules on the surface of a flow cell in clusters, which aids in controlling density of amplicons and makes possible amplification of specific sequence molecules of interest. '200 Patent at 11:3-30, 11:44-12:64, 17:40-67.

C. The '730 Patent

38. The '730 Patent, entitled "Methods and Compositions for Evaluating Genetic Markers," was duly and legally issued by the United States Patent and Trademark Office on December 12, 2023. The inventors of the patent are Dr. Gregory Porreca and Dr. Uri Laserson, and the patent is assigned to Molecular Loop. A copy of the '730 Patent is attached hereto as Exhibit 3.

39. Molecular Loop is the exclusive owner of all rights, title, and interest in the '730 Patent, and has the right to bring this suit to recover damages for any current or past infringement of the '730 Patent. (*See* Ex. 13 ('730 Patent Assignment to Molecular Loop).)

40. Among other things, the '730 Patent claims inventions directed toward the unconventional, non-routine method of incorporating a set of differentiator tags into a sample containing nucleic acid molecules to reduce the impact of errors arising when amplifying and sequencing individual molecules, such as over- or under-representation of one individual molecule during amplification. (*See* '730 Patent at 2:1-67.) For example, Claim 1 recites:

> A method for correcting for errors or bias introduced during nucleic acid analysis workflow, the method comprising the steps of:
> obtaining a biological sample comprising a plurality of target nucleic acid molecules from more than one locus of origin;
> introducing a set of differentiator tags, wherein members of said set of differentiator tags are associated with members of said plurality, such that one or more of said loci of origin are associated with more than one differentiator tag;
> amplifying each of the plurality of tagged target nucleic acid molecules to generate amplicons;
> sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and
> correcting for error or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count.

41. The '730 Patent explains that, *inter alia*, the claimed inventions overcame problems in the field related to systematic and random bias during genome capture, amplification and sequencing, such as a disproportionate representation of heterozygous alleles that may be present after amplification, which could lead to incorrectly identifying a genome as being homozygous instead of heterozygous:

> Aspects of the disclosure are based, in part, on the discovery of methods for overcoming problems associated with systematic and random errors (bias) in genome capture, amplification and sequencing methods, namely high variability in the capture and amplification of nucleic acids and disproportionate representation of heterozygous alleles in sequencing libraries. Accordingly, in some embodiments, the disclosure provides methods that reduce errors associated with the variability in the capture and amplification of nucleic acids. In other embodiments, the methods improve allelic representation in sequencing libraries and, thus, improve variant detection outcomes. In certain embodiments, the disclosure provides preparative methods for capturing target nucleic acids (e.g., genetic loci) that involve the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules. In some embodiments, the differentiator tag sequence permit the detection of bias based on the occurrence of combinations of differentiator tag and target sequences observed in a sequencing reaction. In other embodiments, the methods reduce errors caused by bias, or the risk of bias, associated with the capture, amplification and sequencing of genetic loci, e.g., for diagnostic purposes.

'730 Patent at 4:57-5:11; *see also* Fig. 5.

42. The '730 Patent teaches that one benefit of Molecular Loop's invention is realized by performance of the claimed method, including through tagging individual target nucleic acid molecules with differentiator tag sequences so that individual amplicons could later be traced back to an individual target molecule during data analysis:

> Aspects of the invention relate to associating unique sequence tags (referred to as differentiator tag sequences) with individual target molecules that are independently captured and/or analyzed (e.g., prior to amplification or other process that may introduce bias). These tags are useful to distinguish independent target molecules from each other thereby allowing an analysis to be based on a known

> number of individual target molecules. For example, if each of a plurality of target molecule sequences obtained in an assay is associated with a different differentiator tag, then the target sequences can be considered to be independent of each other and a genotype likelihood can be determined based on this information. In contrast, if each of the plurality of target molecule sequences obtained in the assay is associated with the same differentiator tag, then they probably all originated from the same target molecule due to overrepresentation (e.g., due to biased amplification) of this target molecule in the assay. This provides less information than the situation where each nucleic acid was associated with a different differentiator tag. In some embodiments, a threshold number of independently isolated molecules (e.g., unique combinations of differentiator tag and target sequences) is analyzed to determine the genotype of a subject.

'730 Patent at 28:25-48; *see also id.* at 31:45-32:10.

43. The '730 Patent further describes using read counts of individual target molecules that have been tagged with differentiator tag sequences during data analysis:

> A large library of unique differentiator tag sequences may be created by using degenerate, random-sequence polynucleotides of defined length. The differentiator tag sequences of the polynucleotides may be read at the final stage of the sequencing. The observations of the differentiator tag sequences may be used to detect and correct biases in the final sequencing read-out of the library. For example, the total possible number of differentiator tag sequences, which may be produced, e.g., randomly, is 4N, where N is the length of the differentiator tag sequence. Thus, it is to be understood that the length of the differentiator tag sequence may be adjusted such that the size of the population of MIPs [molecular inversion probes] having unique differentiator tag sequences is sufficient to produce a library of MIP capture products in which identical independent combinations of target nucleic acid and differentiator tag sequence are rare. As used herein combinations of target nucleic acid and differentiator tag sequences, may also be referred to as "target:differentiator tag sequences".
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> …
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> In some embodiments, overrepresentation of target:differentiator tag sequences in a pool of preparative nucleic acids (e.g., amplified MIP capture products) is indicative of bias in the preparative process (e.g., bias in the amplification process). For example, target:differentiator tag sequence combinations that are statistically

> overrepresented are indicative of bias in the protocol at one or more steps between the incorporation of the differentiator tag sequences into MIPs and the actual sequencing of the MIP capture products. The number of reads of a given target:differentiator tag sequence may be indicative (may serve as a proxy) of the amount of that target sequence present in the originating sample. In some embodiments, the numbers of occurrence of sequences in the originating sample is the quantity of interest. For example, using the methods disclosed herein, the occurrence of differentiator tag sequences in a pool of MIPs may be predetermined (e.g., may be the same for all differentiator tag sequences). Accordingly, changes in the occurrence of differentiator tag sequences after amplification and sequencing may be indicative of bias in the protocol. Bias may be corrected to provide an accurate representation of the composition of the original MIP pool, e.g., for diagnostic purposes.

'730 Patent at 29:37-30:18.

44. The '730 Patent explains that its unconventional, non-routine technique overcame problems in the field, such as bias of certain individual molecules during amplification, with a novel and innovative solution – incorporating differentiator tag sequences into the sequences of individual target molecules:

> In some embodiments, the invention relates to compositions comprising pools (libraries) of preparative nucleic acids that each comprise "differentiator tag sequences" for detecting and reducing the effects of bias, and for genotyping target nucleic acid sequences. As used herein, a "differentiator tag sequence" is a sequence of a nucleic acid (a preparative nucleic acid), which in the context of a plurality of different isolated nucleic acids, identifies a unique, independently isolated nucleic acid. Typically, differentiator tag sequences are used to identify the origin of a target nucleic acid at one or more stages of a nucleic acid preparative method. For example, in the context of a multiplex nucleic acid capture reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, target nucleic acid capture events. Also, in the context of a multiplex nucleic acid amplification reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, primary amplicons of a target nucleic acid, for example. Thus, combinations of target nucleic acid and differentiator tag sequence (target:differentiator tag sequences) of an isolated nucleic acid of a preparative method provide a basis for identifying unique, independently isolated target nucleic acids.

'730 Patent at 28:49-29:6; *see also id.* at 29:37-30:18.

DEFENDANTS' INFRINGING ACTIVITIES

45. Molecular Loop incorporates by reference paragraphs 1-44.

A. The Accused Verifi Prenatal Tests

46. VHI first sold the Verifi Prenatal Test, a commercial non-invasive prenatal test, in March 2012. (*See* Ex. 14 (https://www.theatlantic.com/health/archive/2012/03/a-more-accurate-prenatal-test-for-detecting-signs-of-down-syndrome/254264/).) On January 7, 2013, Illumina announced the acquisition of VHI to expand its noninvasive prenatal test offerings with the Verifi Prenatal Test. (*See* Ex. 15 (https://www.genengnews.com/news/illumina-acquires-verinata-health/).) In 2017, Defendants also launched the Verifi Prenatal Plus Test which contains everything in the Verifi Prenatal test with additional panels. (*See* Ex. 16 (*Illumina, Inc. v. Natera, Inc.*, Case No. 3:18-cv-01662-SI, D.I. 63 at 5 (N.D. Cal. Sep. 6, 2018)).) To date, Defendants still offer both the Verifi Prenatal Test and the Verifi Prenatal Plus Test (collectively the "Verifi Tests"). (*See* Ex. 9 (https://www.illumina.com/clinical/illumina_clinical_laboratory/verifi-prenatal-tests.html).)

47. The Verifi Tests "provide the latest innovation in [DNA] sequencing" to "safely and noninvasively screen for the most common chromosomal aneuploidies as early as 10 weeks gestation using a single maternal blood draw." (*See* Ex. 9 (https://www.illumina.com/clinical/illumina_clinical_laboratory/verifi-prenatal-tests.html).) Defendants describe the use of NGS sequencing in the Verifi Test Workflow as shown below:

Figure 1: NGS Workflow for NIPT—To demonstrate the performance of the verifi Prenatal Test on the NextSeq 500 System, experiments using both the NextSeq 500 and HiSeq Systems followed the same workflow.

(Ex. 17 (Application Note: Reproductive and Genetic Health); *see also*, Ex. 18 (Verifi Patient Brochure) ("The verifi Test takes a deeper approach to the science, using an advanced technology called 'Massively Parallel Sequencing' to analyze millions of DNA fragments per sample and count the number of chromosomes present.").)

48. Performance of the Verifi Tests requires incorporating at least two members of a plurality of identifier sequences into template nucleic acids. For example, Illumina publications describe using Illumina DNA Library Prep Kits, such as TruSeq kits, in the Verifi Test workflow. (*See, e.g.*, Ex. 19 at 893 (Bianchi et al.) ("[S]equencing libraries were prepared using Illumina TruSeq kit v2.5."); *See*, Ex. 20 at 3 (Verifi White Paper) ("MPS was performed on the Illumina Hi-Seq 2000 instrument using TruSeqTM v3.0 sequencing chemistry.").)

49. Performance of the Verifi Tests further requires combining nucleic acid templates. For example, publications using the Verifi Test describe using Illumina DNA Library Prep Kits that provide for combining multiple samples together, or sample pooling. (*See* Ex. 21 at 4 (TruSeq DNA Nano Datasheet) ("For the greatest operational efficiency, up to 96 preplated, uniquely indexed samples can be pooled and sequenced together in a single flow cell lane on any Illumina sequencing platform."); *see also* Ex. 22 at 2 (Illumina DNA Prep Sheet) ("Seqeuncing-ready fragments are washed and pooled.").)

50. Performance of the Verifi Tests further requires amplifying nucleic acid templates on a surface of a flow cell. For example, the Verifi Tests are run on Illumina sequencers that use flow cell technology to form clusters through DNA amplification. (*See, e.g.*, Ex. 19 at 893 (Bianchi et al.) ("[S]equencing libraries were prepared using Illumina TruSeq kit v2.5 and sequencing (6-plax, ie, 6 samples/lane) was performed on an Illumina HiSeq 2000 instrument in the Verinata Health Laboratory.")).

51. Performance of the Verifi Tests further requires sequencing amplicons. For example, the Verifi Tests are run on Illumina sequencers such as the HiSeq sequencers. (*See, e.g.*, Ex. 17 (Application Note: Reproductive and Genetic Health) ("The Illumina HiSeq and NextSeq 500 NGS Sequencing Systems provide the throughput, read length, and depth required for NIPT."); Ex. 19 (Bianchi et al.) (using "Illumina HiSeq 2000" as the sequencer in the Verifi Test workflow).)

52. Performance of the Verifi Tests further requires discarding sequence reads obtained in said sequencing step that contain incorrect combinations of identifier sequences. For example, the Verifi Tests require a data analysis step that includes demultiplexing samples. (*See* Ex. 17 (Application Note: Reproductive and Genetic Health) ("Demultiplex samples" listed in the Data Analysis step of the Verifi Tests workflow). The Verifi Tests use Illumina software, such as bcl2fastq2 Conversion Software, to discard sequence reads that are different than any of the original distinct pairs, or demultiplex samples. (*See* Ex. 23 at 12 (bcl2fast2Q conversion Software v2.20 Software Guide) ("When a sample sheet contains multiplexed samples, the software: Places reads without a matching index adapter sequencer in the Undetermined_S0 FASTQ file. Places reads with a valid index adapter sequencers in the sample FASTQ file.").)

B. The Accused VeriSeq Tests

53. Illumina launched the VeriSeq NIPT solution in April 2017. (Ex. 24 (https://www.illumina.com/company/news-center/press-releases/press-release-details.html?newsid=d6bf8efa-3be8-45a8-8f41-450b4e531002).) Defendants developed and launched the VeriSeq NIPT Solution v2 in June 2019. (Ex. 25 (https://www.illumina.com/company/news-center/press-releases/press-release-details.html?newsid=8e4a1ea5-47f8-4bb4-b061-c07275fb0070).) Defendants still offer the VeriSeq NIPT Solution v2 for sale and provide documentation for both the VeriSeq NIPT solution and the VeriSeq NIPT solution v2 (collectively the "VeriSeq Tests"). (*See, e.g.*, Ex. 26 (https://www.illumina.com/products/by-type/ivd-products/veriseq-nipt.html#tabs-f8e99fd41a-item-caa762b6ab-documentation).) The VeriSeq Tests are purchased and distributed in the United States. (*See, e.g.*, Ex. 27 (https://www.aruplab.com/testing/nipt) ("ARUP's test is performed on the Illumina VeriSeq NIPT Solution platform, which uses massively parallel whole genome sequencing of cell-free DNA (cfDNA) derived from maternal whole blood samples.").)

54. The VeriSeq Tests are "in vitro diagnostic test[s] intended for use as a screening test for the detection of genome-wide anomalies from maternal peripheral whole blood specimens in pregnant women of at least 10 weeks gestation." (Ex. 28 (VeriSeq NIPT Solution v2 Package Insert).)

55. The VeriSeq Tests require incorporating at least two members of a plurality of identifier sequences into template nucleic acids. For example, the VeriSeq Tests require the use of unique indexed adapters in the Library Preparation step. (*See* Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) ("Each sample in a set of 24, 48, or 96 receives a unique indexed adapter."); *see also id.* at 10 (Requiring a next generation sequencer that is "[c]ompatible with VeriSeq NIPT Sample Prep dual index adapters").)

56. The VeriSeq Tests further require combining nucleic acid templates. For example, Illumina documents require a library pooling step. (*See*, *e.g.*, Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) ("The sample libraries are pooled together into 24- or 48- sample pool in adjusted amounts to minimize variation in coverage."); Ex. 29 at 1212 (Pertile et al.) ("The indexed adapters allowed sample identification and contained sequences that allowed for library capture on the solid surface of a sequencing flow cell for cluster generation and subsequent sequencing. Individual libraries were quantified before pooling.").)

57. The VeriSeq Tests further require amplifying nucleic acid templates on a surface of a flow cell. For example, the VeriSeq Tests include the use of next generation sequencers that utilize flow cell technology, such as Illumina Sequencers. (*See, e.g.*, Ex. 29 (Pertile et al.) ("Sequencing was carried out using a NextSeq 550Dx instrument (Illumina) and the NextSeq 550Dx Reagent Kit v2.5 (Illumina)."); *see also* Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) ("Index adapters contain sequences that allow for library capture on the solid surface of a *sequencing flow cell* for cluster generation and subsequent sequencing.") (emphasis added), at 10 (requiring a next generation sequencing system compatible with dual index adapters that allow for library capture on the solid surface of a sequencing flow cell).)

58. The VeriSeq Tests further require sequencing amplicons. For example, performance of the VeriSeq Tests requires using a NGS system, such as an Illumina sequencer, to sequence DNA samples. (*See*, Ex. 29 (Pertile et al.) ("Sequencing was carried out using a NextSeq 550Dx instrument (Illumina) and the NextSeq 550Dx Reagent Kit v2.5 (Illumina)."); *see also*, Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) ("The sample libraries are pooled together into 24- or 48- sample pool in adjusted amounts to minimize variation in coverage. Each sample is then sequenced using a next-generation sequencing system.").)

59. The VeriSeq Tests further require discarding sequence reads obtained in said sequencing step that contain incorrect combinations of identifier sequences. For example, Illumina's VeriSeq materials describe demultiplexing sequencing data. (*See* Ex. 28 at 35 (VeriSeq NIPT Solution v2 Package Insert) ("After sequencing data are collected, they are demultiplexed, converted to a FASTQ format, aligned to a reference genome, and analyzed for aneuploidy detection."), at 3 ("Indexes allow sample identification in subsequent sequencing …Identification of library fragments by index sequence and alignment of the paired end reads to a human reference genome.").)

60. On information and belief, Illumina licenses the right to perform VeriSeq Tests to third party laboratories. For example, Illumina licenses the VeriSeq NIPT v2 Solution Software required for the VeriSeq Tests to end users. (*See* Ex. 30 at 24 (VeriSeq NIPT Solution v2 Software Product Documentation) ("When you first log in to the web UI, you are requested to accept the End User License Agreement (EULA).…The software requires you to accept the EULA before you can continue working with the web UI.").)

61. Illumina has continuous contact and control over the VeriSeq Tests and its users. For example, Illumina provides trainings, site inspections, and continuing support to third-party laboratories and other users of the VeriSeq Tests. (*See, e.g.*, Ex. 10 (https://www.illumina.com/products/by-type/ivd-products/veriseq-nipt.html).) Illumina Field Service Engineers are assigned the user role of "Service" in the VeriSeq system software and are available to "troubleshoot[], perform[], service repair, set[] up and change configuration settings, and provide[] ongoing support." (Ex. 30 at 27 (VeriSeq NIPT Solution v2 Software Product Documentation).) Illumina Technical Support updates the Assay Software and Onsite Servers that are part of the VeriSeq Tests. (*Id.* at 39.) On information and belief, Illumina also keeps stored

data of VeriSeq systems. (*Id.* ("The database can be restored from any given backup snapshot. Restores are done by Illumina Field Service Engineers only.").) Illumina also provides consumable materials required to perform the VeriSeq Tests to third-party laboratories and other users of the VeriSeq Tests. (*See* Ex. 28 at 4-9 (VeriSeq NIPT Solution v2 Package Insert).)

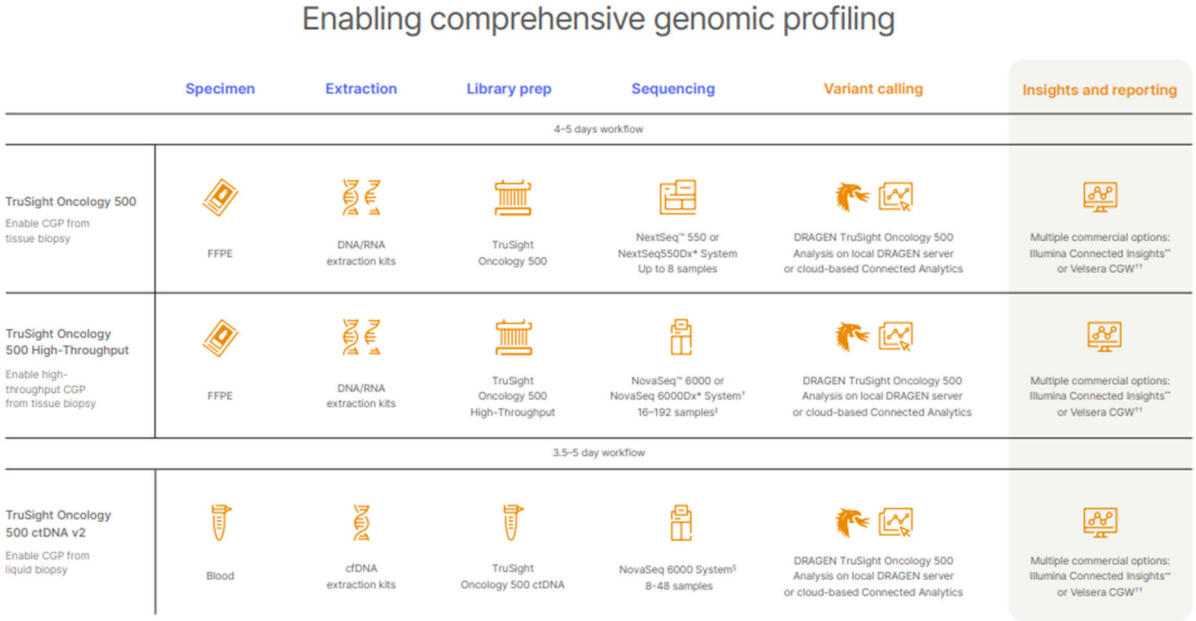
62. Illumina instructs users to use the VeriSeq Tests as described above, for example, by providing installation, instructions, product manuals, package inserts, checklists, and competency testing to their customers and third-party laboratories. (*See, e.g.*, Ex. 10 (https://www.illumina.com/products/by-type/ivd-products/veriseq-nipt.html).)

63. Illumina promotes the use of the VeriSeq Tests as described above by "provid[ing] everything needed to run the assay with scalable workflow." (*Id.*) For example, Illumina's VeriSeq software guides the user through every step of performing the VeriSeq Tests. (*See, e.g.*, Ex. 30 (VeriSeq NIPT Solution v2 Software Product Documentation).)

C. The Accused TruSight Tests

64. On October 30, 2018, Illumina launched TruSight Oncology 500 (the "TSO 500" test), a pan-cancer assay made to identify biomarkers in tumors. (Ex. 31 (https://www.illumina.com/company/news-center/press-releases/2018/2374252.html).) On November 5, 2019, Illumina announced the launch of TruSight Oncology 500 ctDNA (the "TSO 500 ctDNA" test) and TruSight Oncology 500 High-Throughput (the "TSO 500 HT" test), liquid biopsy assays designed to detect cancer biomarkers. (Ex. 32 (https://www.illumina.com/company/news-center/feature-articles/TSO-500-NovaSeq.html).)

65. Illumina offers TSO 500, TSO 500 ctDNA v2, and TSO500 HT (collectively the "TSO 500 Tests") for sale on Illumina's website. (*See, e.g.*, Ex. 33 (https://www.illumina.com/products/by-brand/trusight-oncology/tso-500-portfolio.html); Ex. 34 at 9 (TruSight Oncology 500 Portfolio Brochure).) The TSO500 Tests "[a]nalyze multiple variant types and key biomarkers in 523 cancer-relevant genes across DNA" in the workflows below: (Ex. 34 at 6-9 (TruSight Oncology 500 Portfolio Brochure).)



66. The TSO 500 Tests require obtaining a biological sample comprising a plurality of target nucleic acid molecules. For example, the TSO500 ctDNA test uses cell-free DNA in blood plasma. (*See*, *e.g.*, Ex. 35 at 2 (TruSight Oncology 500 ctDNA Product Data Sheet) ("Cell-free DNA is extracted from plasma"), at 4 ("TruSight Oncology 500 ctDNA enables comprehensive genomic profiling from just 30 ng of cfDNA, making it an ideal alternative for use when tissue is not readily available or as a complement to tissue analysis."). The TSO 500 and TSO 500 HT tests require DNA or RNA from tissue samples. (*See, e.g.*, Ex. 36 at 1 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) ("Enabling flexible, scalable comprehensive genomic

profiling from FFPE samples."), at 2 ("Minimum recommendation of 2 mm from FFPE tissue samples.").)

67. The TSO 500 Tests further require introducing a set of differentiator tags. For example, the TSO 500 Tests require a library preparation step that ligates unique molecular identifiers to DNA sample. (*See* Ex. 35 at 1 (TruSight Oncology 500 ctDNA Product Data Sheet) ("Library preparation incorporates unique molecular identifiers (UMIs) that enable ultra-low frequency variant identification."), at 5 ("To enable ultra-low frequency variant identification, library preparation takes advantage of target enrichment with biotinylated probes and streptavidin-coated magnetic beads to enrich for selected DNA-based libraries and unique molecular identifiers (UMIs) to reduce error rates."), at 6 (showing figure ligating UMI adapters to DNA); *see also*, Ex. 36 at 6 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) ("During library preparation, unique molecular identifiers (UMIs) are added to gDNA or cDNA fragments. These UMIs enable detection of variants at low variant allele frequency (VAF) while simultaneously suppressing errors, providing high analytical specificity."), at 8 ("The addition of UMIs during library preparation coupled with proprietary Illumina informatics reduces sequencing error rates by 10-20 fold."); Ex. 37 at 1 (TruSight Oncology UMI Reagents Products Data Sheet) ("Error correction with unique molecular identifiers (UMIs) for sequencing libraries."), *id.* ("Illumina offers the TruSight Oncology UMI Reagents, which implement UMIs and error correction software to lower the rate of inherent errors in NGS data. The UMI reagents integrate easily with the TruSight Oncology workflow by simply replacing standard Y-shaped adapters with UMI-containing adapters to barcode each individual DNA strand."), at 2 (depicting error correction with UMIs).)

68. The TSO 500 Tests further require amplifying each of the plurality of tagged target nucleic acid molecules. For example, each of the TSO 500 Tests are sequenced on Illumina Sequencers, such as the NovaSeq 6000 system or NextSeq 550, which amplify DNA molecules on the surface of a flow cell before sequencing the amplified DNA molecules. (*See* Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).)

69. The TSO 500 Tests further require correcting for error or bias. For example, TSO 500 Tests include software the performs error correction by collapsing sequencing reads. (*See* Ex. 35 at 4 (TruSight Oncology 500 ctDNA Product Data Sheet) ("DRAGEN TruSight Oncology 500 ctDNA Analysis Software uses accelerated, fully integrated bioinformatics algorithms to ensure optimal assay performance. The software performs sequence alignment, error correction by collapsing the sequence, then variant calling based on the raw data. Duplicated reads and sequencing errors are removed without losing signal for low-frequency variants while yielding high-sensitivity variant calling results."); *see also* Ex. 36 at 7 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) ("Variant calling for TruSight Oncology 500 and TruSight Oncology 500 High-Throughput is available with DRAGEN secondary analysis either on premise using a local DRAGEN Server or in the cloud using Illumina Connected Analytics (ICA), now with data streaming and autolaunch capabilities. Both versions take advantage of sophisticated, proprietary algorithms that remove errors, artifacts, and germline variants."); Ex. 37 at 1 (TruSight

Oncology UMI Reagents Products Data Sheet) ("Error correction with unique molecular identifiers (UMIs) for sequencing libraries."), at 2 ("After UMI-containing libraries are sequenced, the UMI Error Correction App aligns reads, then collapses the sequences with shared UMIs down to unique reads (Figure 3). This process enables the filtering of false positives, which are excluded from the collapsed reads, reducing the error rate for variant calling."); Ex. 39 at 2 (DRAGEN Analysis Workflows Webpage) (The alignment step [for the TSO 500 ctDNA Test] uses DRAGEN Aligner with UMI collapsing to align DNA sequences in FASTQ files to the hg19_decoy genome. This step combines sets of reads (ie, families) that are grouped together based on genomic locations and UMI tags into representative sequences. This process accurately removes duplicate reads and sequencing errors without losing the signal of very low frequency (<1%) sequence variations."), at 6 ("DNA alignment and error correction involves aligning sequencing reads derived from DNA libraries to a reference genome and correcting errors in the sequencing reads prior to variant calling.…Reads from the same original DNA molecule are tagged with the same UMI during library preparation [of the TSO 500 test]. The UMI allows DRAGEN to compare related reads, remove outlier signals, and collapse multiple reads into a single high-quality sequencing.").)

70. The TSO 500 Tests also require incorporating at least two members of a plurality of identifier sequences into template nucleic acids. For example, the TSO 500 Tests incorporate dual index adapters in the library preparation step. (*See* Ex. 40 at 11 (TruSight Oncology 500 ctDNA Reference Guide) ("In this step, library fragments are amplified using primers that add index sequences for sample multiplexing. The resulting product contains the complete library of cfDNA fragments flanked by index sequences and adapters for cluster generation."), at 12 ("When sequencing multiple libraries on a single flow cell, assign a different indexing primer to each sample library. Record sample layout orientation and the indexes for each sample library."); Ex.

41 at 46-51 (Illumina Adapter Sequences Data Sheet) (listing dual index adapters to be used with TSO 500 tests).)

71. The TSO 500 Tests further require combining nucleic acid templates. For example, the TSO 500 Tests pool DNA libraires together to be sequenced together. (*See* Ex. 42 at 47 (TruSight Oncology 500 Reference Guide) ("See the denature and dilute libraries guide for the sequencing system to pool, denature, and dilute libraries to the loading concentration."); Ex. 40 at 29 (TruSight Oncology 500 ctDNA Reference Guide) ("See the system for your sequencing system to pool, denature, and dilute libraries to the loading concentration."); Ex. 38 at 3 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) (specifying sample throughput of 8, 24, or 48 samples); Ex. 39 at 5 (DRAGEN Analysis Workflows Webpage) ("Sequencing data [for the TSO 500 test] stored in BCL format are demultiplexed through a process that uses the index sequences unique to each sample to assign clusters to the library from which they originated. Each cluster contains two indexes (i7 and i5 sequences, one at each end of the library fragment). The combination of those index sequences are used to demultiplex the pooled libraries. After demultiplexing, this process generates FASTQ files, which contain sequencing reads for each individual sample library and the associated quality scores for each base call, excluding from any clusters that did not pass filter.").)

72. The TSO 500 Tests further require amplifying nucleic acid templates on a surface of a flow cell. For example, the TSO 500 Tests are sequenced on Illumina Sequencers, such as the NovaSeq 6000 system or NextSeq 550, which amplify DNA molecules on the surface of a flow cell before sequencing the amplified DNA molecules. (*See* Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X

Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).)

73. The TSO 500 Tests further require sequencing amplicons. For example, performance of the TSO 500 Tests requires using a NGS system, such as an Illumina sequencer, to sequence DNA samples. (*See* Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).)

74. The TSO 500 Tests further require discarding sequence reads obtained in said sequencing step that contain incorrect combinations of identifier sequences. For example, the TSO 500 Tests include software that demultiplexes DNA sequence reads. (*See* Ex. 39 at 5 (DRAGEN Analysis Workflows Webpage) ("Sequencing data [for the TSO 500 test] stored in BCL format are demultiplexed through a process that uses the index sequences unique to each sample to assign clusters to the library from which they originated. Each cluster contains two indexes (i7 and i5 sequences, one at each end of the library fragment). The combination of those index sequences are used to demultiplex the pooled libraries. After demultiplexing, this process generates FASTQ files, which contain sequencing reads for each individual sample library and the associated quality scores for each base call, excluding from any clusters that did not pass filter."); *see also* Ex. 38 at

3 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) (specifying sample throughput of 8, 24, or 48 samples).)

75. On information and belief, Illumina licenses the right to perform TSO 500 Tests to third party laboratories. For example, Illumina licenses the TSO 500 analysis software used to perform the TSO 500 workflow. (*See, e.g.*, Ex. 43 (https://support.illumina.com/content/dam/illumina-support/documents/documentation/software_documentation/trusight/trusight-oncology-500/DRAGEN%20TSO500%20and%20HRD%20RUO%20EULA%20(March%2028%202023).pdf).)

76. On information and belief, Illumina has continuous contact and control over the TSO 500 Tests and its users. For example, Illumina provides trainings, site inspections, and continuing support to third-party laboratories and other users of the TSO 500 Tests. (*See, e.g.*, Ex. 44 (https://support.illumina.com/sequencing/sequencing_kits/trusight-oncology-500.html); *see also* Ex. 34 at 19 (TruSight Oncology 500 Portfolio Brochure) ("Our scientists and engineers are ready to assist with instrument installation and laboratory setup. In addition to onsite support, courses are available to train users on various workflows. Illumina scientists are available 24 hours a day, five days a week globally to answer questions every step of the way.").)

77. Illumina instructs users to use the TSO 500 Tests as described above, for example, by providing installation, instructions, product manuals, package inserts, checklists, and competency testing to their customers and third-party laboratories. (*See, e.g.*, Ex. 44 (https://support.illumina.com/sequencing/sequencing_kits/trusight-oncology-500.html).) On information and belief, the documentation and instructions Illumina provides to its users include the use of the TSO 500 Tests for analysis.

78. Illumina promotes the use of the TSO 500 Tests as described above by providing a "streamlined workflow using proven NGS technology that enables rapid, reliable CGP." (Ex. 34 at 8 (TruSight Oncology 500 Portfolio Brochure).) For example, Illumina provides reference guides that instruct the user through every step of performing the TSO 500 Tests. (*See, e.g.*, Ex. 45 (https://support.illumina.com/sequencing/sequencing_kits/trusight-oncology-500/documentation.html).)

D. Defendants' Knowledge of Molecular Loop's Patents

79. The Patents-in-Suit claim advancements in the genetic sequencing industry in which Defendants actively participate, and are breakthroughs in genome sequencing. On information and belief, Defendants have been aware of the Patents-in-Suit and the fact that performance of the Defendants' Accused Products practice the claimed inventions of those patents since at least February 2023, when Dr. Porreca and Illumina began discussing Molecular Loop's technology and patents.

80. Defendants have been and are the assignee of a number of patents and patent applications that are related to subject matter similar to that in the Patents-in-Suit and that were filed after the Patents-in-Suit were published. On information and belief, in researching the patentability of its own patents, Illumina did become aware of the '852 Patent by at least February 2021 and the '200 Patent by at least September 2021, when the applications for each were published, and the '730 Patent by at least December 2023, when the patent was issued.

81. Defendants have additionally been aware of the Patents-in-Suit and the fact that performance of Defendants' Accused Products practice the claimed inventions of those patents since at least December 2023 through communications with Molecular Loop identifying the Patents-in-Suit and Defendants' infringement of the patents.

82. Despite its knowledge of the Patents-in-Suit and of its infringement of each, Defendants have continued to willfully infringe the Patents-in-Suit so as to obtain significant benefits of Molecular Loop's innovations without paying compensation to Molecular Loop. For example, Defendants have continued to use the claimed methods in each of the infringing products without a license, and, on information and belief, has generated millions of dollars in revenue from its infringement. Additionally, after becoming aware of the Patents-in-Suit through at least its discussions with Dr. Porreca and other Molecular Loop representatives, Defendants have proceeded to commercialize the infringing products built on and including the claimed inventions of the Patents-in-Suit without entering into any licenses.

COUNT I

(Infringement Of The '852 Patent)

83. Paragraphs 1 through 82 are incorporated by reference as if fully stated herein.

84. The '852 patent is valid and enforceable.

85. Defendants have infringed, and continue to infringe, one or more claims of the '852 patent under 35 U.S.C. § 271, either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including at least Defendants' Verifi Tests, VeriSeq Tests, and TSO 500 Tests.

86. As one example, Defendants infringe at least claim 1 of the '852 patent by using the Verifi Tests. For example, use of the Verifi Tests require a method for reducing template cross-over error introduced during sequencing workflow, the method comprising the steps of:

a. incorporating at least two members of a plurality of identifier sequences (such as dual indexes) into template nucleic acids (such as DNA) obtained from at least two

different samples, wherein said two members constitute a distinct pair associated with said template (*see, e.g.*, Ex. 19 at 893 (Bianchi et al.) ("[S]equencing libraries were prepared using Illumina TruSeq kit v2.5."); *see*, Ex. 20 (Verifi White Paper) ("MPS was performed on the Illumina Hi-Seq 2000 instrument using TruSeqTM v3.0 sequencing chemistry.”));

b. combining said nucleic acid templates into a single sample (*see* Ex. 21 at 4 (TruSeq DNA Nano Datasheet) ("For the greatest operational efficiency, up to 96 preplated, uniquely indexed samples can be pooled and sequenced together in a single flow cell lane on any Illumina sequencing platform."); *see also* Ex. 22 at 2 (Illumina DNA Prep Sheet) ("Seqeuncing-ready fragments are washed and pooled.");

c. amplifying said nucleic acid templates on a surface of a flow cell thereby to form clusters, at least one of which comprises a chimeric sequence comprising a combination of identifier sequences that are different than any of said distinct pairs (*see, e.g.*, Ex. 19 at 893 (Bianchi et al.) ("[S]equencing libraries were prepared using Illumina TruSeq kit v2.5 and sequencing (6-plax, ie, 6 samples/lane) was performed on an Illumina HiSeq 2000 instrument in the Verinata Health Laboratory");

d. sequencing amplicons obtained in said amplifying step (*see, e.g.*, Ex. 17 (Application Note: Reproductive and Genetic Health) ("The Illumina HiSeq and NextSeq 500 NGS Sequencing Systems provide the throughput, read length, and depth required for NIPT."); Ex. 19 (Bianchi et al.) (using "Illumina HiSeq 2000" as the sequencer in the Verifi Test workflow); and

e. discarding sequence reads obtained in said sequencing step that contain said combination of identifier sequences that are different than any of said distinct pairs, thereby to reduce cross-over error (*see* Ex. 17 (Application Note: Reproductive and Genetic Health) ("Demultiplex samples" listed in the Data Analysis step of the Verifi Tests workflow); Ex. 23 at 12 (bcl2fast2Q conversion Software v2.20 Software Guide) ("When a sample sheet contains multiplexed samples, the software: Places reads without a matching index adapter sequencer in the Undetermined_S0 FASTQ file. Places reads with a valid index adapter sequencers in the sample FASTQ file.").).

87. Defendants have infringed, and continue to infringe, one or more claims of the '852 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Verifi Tests either themselves and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Verifi Tests. For example, Defendants use the Verifi Tests by collecting and analyzing samples sent to Defendants' laboratories for processing. (*See* Ex. 9 (https://www.illumina.com/clinical/illumina_clinical_laboratory/verifi-prenatal-tests.html) ("Physicians can order this Illumina service through our network of partner labs. Samples are processed at our CLIA-certified, CAP-accredited lab within 3-5 days. The physician will receive a report for use in discussing results and next steps with the patient….The Verifi Prenatal Test was developed by, and its performance characteristics were determined by Verinata Health, Inc. (VHI), a wholly owned subsidiary of Illumina, Inc. The VHI laboratory is CAP-accredited[.]").) On information and belief, Illumina has the right and the ability to direct and control the activities of VHI in several ways, including through Illumina's 100% ownership of VHI, through instituting programs and measures (such as policies and protocols) at VHI, and

through interim instructions via at least Illumina's employees and/or officers who hold leadership roles at VHI. Further, VHI acts on behalf of Illumina, including when VHI performs tests on Illumina's behalf for Illumina's patients, or provides test results to health care providers and/or patients on Illumina's behalf. (*Id.*).

88. In addition or in the alternative, Defendants have also induced infringement, and continue to induce infringement, of one or more of the claims of the '852 Patent under 35 U.S.C. § 271(b). Defendants actively, knowingly, and intentionally induce infringement of the '852 Patent by selling or otherwise supplying the Verifi Tests to third-party laboratories with the knowledge and intent that the third-party laboratories will use the Verifi Tests supplied by Defendants to infringe the '852 Patent. Defendants act with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the Verifi Tests and/or the creation and dissemination of supporting materials, instructions, manuals, guides, and/or technical information related to the Verifi Tests.

89. Defendants specifically intend and are aware that the ordinary and customary use of the Verifi Tests by their customers and partners would infringe the '852 Patent. For example, Defendants sell and provide the Verifi Tests, which when used in their ordinary and customary manner intended and instructed by Defendants, infringe one or more claims of the '852 Patent, including at least claim 1. On information and belief, Defendants further provide product manuals and other instruction materials that cause their customers and partners to operate the Verifi Tests for their ordinary and customary use. (*See, e.g.*, Ex. 9 (https://www.illumina.com/clinical/illumina_clinical_laboratory/verifi-prenatal-tests.html) ("Physicians can order this Illumina service through our network of partner labs.").) Defendants accordingly induce third parties to use Verifi Tests in their ordinary and customary way to infringe

the ’852Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the ’852 Patent.

90. In addition or in the alternative, Defendants contribute to the infringement by third parties, such as health care providers or laboratories of one or more of the claims of the ’852 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Verifi Tests knowing that those products constitute a material part of the inventions of the ’852 Patent, knowing that those products are especially made or adapted to infringe the ’852 Patent and knowing that those products are not staple article of commerce suitable for substantial non-infringing use.

91. As another example, Defendants infringe at least Claim 1 of the ’852 Patent by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, the VeriSeq Tests and TSO 500 Tests. For example, use of the VeriSeq Tests and TSO 500 Tests require a method for reducing template cross-over error introduced during sequencing workflow, the method comprising the steps of:

a. incorporating at least two members of a plurality of identifier sequences (such as dual indexes) into template nucleic acids (such as DNA) obtained from at least two different samples, wherein said two members constitute a distinct pair associated with said template (*see* Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) (“Each sample in a set of 24, 48, or 96 receives a unique indexed adapter.”), at 10 (Requiring a next generation sequencer that is “[c]ompatible with VeriSeq NIPT Sample Prep dual index adapters”); Ex. 40 at 11 (TruSight Oncology 500 ctDNA Reference Guide) (“In this step, library fragments are amplified using primers that add index sequences for sample multiplexing. The resulting product contains the

complete library of cfDNA fragments flanked by index sequences and adapters for cluster generation."), at 12 ("When sequencing multiple libraries on a single flow cell, assign a different indexing primer to each sample library. Record sample layout orientation and the indexes for each sample library."); Ex. 41 at 46-51 (Illumina Adapter Sequences Data Sheet) (listing dual index adapters to be used with TSO 500 tests).);

b. combining said nucleic acid templates into a single sample (s*ee*, *e.g.*, Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) ("The sample libraries are pooled together into 24- or 48- sample pool in adjusted amounts to minimize variation in coverage."); Ex. 29 at 1212 (Pertile et al.) ("The indexed adapters allowed sample identification and contained sequences that allowed for library capture on the solid surface of a sequencing flow cell for cluster generation and subsequent sequencing. Individual libraries were quantified before pooling."); Ex. 42 at 47 (TruSight Oncology 500 Reference Guide) ("See the denature and dilute libraries guide for the sequencing system to pool, denature, and dilute libraries to the loading concentration."); Ex. 40 at 29 (TruSight Oncology 500 ctDNA Reference Guide) ("See the system for your sequencing system to pool, denature, and dilute libraries to the loading concentration."); Ex. 38 at 3 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) (specifying sample throughput of 8, 24, or 48 samples);

c. amplifying said nucleic acid templates on a surface of a flow cell thereby to form clusters, at least one of which comprises a chimeric sequence comprising a combination of identifier sequences that are different than any of said distinct pairs (*see, e.g.*, Ex. 29 (Pertile et al.) ("Sequencing was carried out using a NextSeq

550Dx instrument (Illumina) and the NextSeq 550Dx Reagent Kit v2.5 (Illumina)."); *See*, Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).);

d. sequencing amplicons obtained in said amplifying step (*see, e.g.*, Ex. 29 (Pertile et al.) ("Sequencing was carried out using a NextSeq 550Dx instrument (Illumina) and the NextSeq 550Dx Reagent Kit v2.5 (Illumina)."); *See*, Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).); and

e. discarding sequence reads obtained in said sequencing step that contain said combination of identifier sequences that are different than any of said distinct pairs, thereby to reduce cross-over error (*see, e.g.*, Ex. 28 at 35 (VeriSeq NIPT Solution v2 Package Insert) ("After sequencing data are collected, they are demultiplexed, converted to a FASTQ format, aligned to a reference genome, and analyzed for

aneuploidy detection."), at 3 ("Indexes allow sample identification in subsequent sequencing …Identification of library fragments by index sequence and alignment of the paired end reads to a human reference genome."); Ex. 39 at 5 (DRAGEN Analysis Workflows Webpage) ("Sequencing data [for the TSO 500 test] stored in BCL format are demultiplexed through a process that uses the index sequences unique to each sample to assign clusters to the library from which they originated. Each cluster contains two indexes (i7 and i5 sequences, one at each end of the library fragment). The combination of those index sequences are used to demultiplex the pooled libraries. After demultiplexing, this process generates FASTQ files, which contain sequencing reads for each individual sample library and the associated quality scores for each base call, excluding from any clusters that did not pass filter.").).

92. Defendants have infringed, and continue to infringe, one or more claims of the '852 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Accused Products either themselves and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Accused Products.

93. In addition or in the alternative, Defendants have induced infringement, and continue to induce infringement, of one or more of the claims of the '852 Patent under 35 U.S.C. § 271(b). Defendants actively, knowingly, and intentionally induce infringement of the '852 Patent by selling or otherwise supplying the VeriSeq Tests and TSO 500 Tests to third-party laboratories with the knowledge and intent that the third-party laboratories will use the VeriSeq Tests and TSO 500 Tests supplied by Defendants to infringe the '852 Patent. Defendants act with the knowledge and intent to encourage and facilitate third-party infringement through the

dissemination of the VeriSeq Tests and TSO 500 Tests and/or the creation and dissemination of supporting materials, instructions, manuals, guides, and/or technical information related to the VeriSeq Tests and TSO 500 Tests.

94. Defendants specifically intend and are aware that the ordinary and customary use of the VeriSeq Tests and TSO 500 Tests would infringe the '852 Patent. For example, Defendants sell and provide the VeriSeq Tests and TSO 500 Test, which when used in their ordinary and customary manner intended and instructed by Illumina, infringe one or more of the claims of the '852 Patent, including at least claim 1. On information and belief, Defendants further provide product manuals, guides, and other instructional materials that cause their customers and partners to operate the VeriSeq Tests and TSO 500 Tests for their ordinary and customary use. Defendants accordingly induce third parties to use the VeriSeq Tests and TSO 500 Tests in their ordinary and customary way to infringe the '852 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '852 Patent.

95. In addition or in the alternative, Defendants contribute to the infringement by third parties, such as health care providers or laboratories of one or more of the claims of the '852 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the VeriSeq and TSO 500 Tests knowing that those products constitute a material part of the inventions of the '852 Patent, knowing that those products are especially made or adapted to infringe the '852 Patent and knowing that those products are not staple article of commerce suitable for substantial non-infringing use.

96. Defendants have had knowledge of and notice of the '852 Patent and their infringement since at least February 10, 2023.

97. Defendants' infringement of the '852 Patent was, and continues to be, willful and deliberate since at least February 10, 2023.

98. Molecular Loop has been and continues to be damaged by Defendants' infringement of the '852 patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

99. Defendants' conduct in infringing the '852 patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

COUNT 2

(Infringement Of The '200 Patent)

100. Paragraphs 1 through 99 are incorporated by reference as if fully stated herein.

101. The '200 patent is valid and enforceable.

102. Defendants have infringed, and continue to infringe, one or more claims of the '200 patent under 35 U.S.C. § 271, either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including at least Defendants' Verifi Tests, VeriSeq Tests, and TSO 500 Tests.

103. As one example, Defendants infringe at least claim 1 of the '200 patent by using the Verifi Tests. For example, use of the Verifi Tests require a method for validating the sequence of a nucleic acid analyte of interest in a multiplex sequencing reaction, the method comprising:

a. detecting the presence of two or more identifier sequences (such as dual indexes) that are uniquely associated with the nucleic acid analyte of interest (such as a DNA sample), wherein at least a first identifier sequence is incorporated into a 5' portion of the nucleic acid analyte of interest and wherein at least a second identifier sequence is incorporated into a 3' portion of the nucleic acid analyte of interest, and

wherein the first and second identifier sequences have four or more nucleotides and are different (*see, e.g.*, Ex. 19 at 893 (Bianchi et al.) ("[S]equencing libraries were prepared using Illumina TruSeq kit v2.5 and sequencing (6-plex, ie, 6 samples/lane) was performed on an Illumina HiSeq 2000 instrument in the Verinata Health Laboratory."); *see*, Ex. 20 (Verifi White Paper) ("MPS was performed on the Illumina Hi-Seq 2000 instrument using TruSeqTM v3.0 sequencing chemistry.").);

b. sequencing the first identifier sequence, the nucleic acid analyte of interest and the second identifier sequence (*see, e.g.*, Ex. 17 (Application Note: Reproductive and Genetic Health) ("The Illumina HiSeq and NextSeq 500 NGS Sequencing Systems provide the throughput, read length, and depth required for NIPT."); Ex. 19 (Bianchi et al.) (using "Illumina HiSeq 2000" as the sequencer in the Verifi Test workflow).); and

c. validating the sequence of the nucleic acid analyte of interest by analyzing both identifiers and excluding the sequences of those nucleic acid analytes of interest containing only one identifier or an incorrect pair of identifiers from sequence analysis of the multiplex sequencing reaction (*see, e.g.*, Ex. 21 at 4 (TruSeq DNA Nano Data Sheet) ("After sequencing, the indexes are used to demultiplex the data and accurately assign reads to the proper samples in the pool….Using UDI combinations is a best practice to make sure that reads with incorrect indexes do not impact variant calling."); Ex. 17 (Application Note: Reproductive and Genetic Health) ("Demultiplex samples" listed in the Data Analysis step of the Verifi Tests workflow); Ex. 23 at 12 (bcl2fast2Q conversion Software v2.20 Software Guide) ("When a sample sheet contains multiplexed samples, the software: Places reads

without a matching index adapter sequencer in the Undetermined_S0 FASTQ file. Places reads with a valid index adapter sequencers in the sample FASTQ file.").).

104. Defendants have infringed, and continue to infringe, one or more claims of the '200 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Verifi Tests either themselves and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Verifi Tests. For example, Defendants use the Verifi Tests by collecting and analyzing samples sent to Defendants' laboratories for processing. (*See* Ex. 9 (https://www.illumina.com/clinical/illumina_clinical_laboratory/verifi-prenatal-tests.html) ("Physicians can order this Illumina service through our network of partner labs. Samples are processed at our CLIA-certified, CAP-accredited lab within 3-5 days. The physician will receive a report for use in discussing results and next steps with the patient….The Verifi Prenatal Test was developed by, and its performance characteristics were determined by Verinata Health, Inc. (VHI), a wholly owned subsidiary of Illumina, Inc. The VHI laboratory is CAP-accredited[.]").) On information and belief, Illumina has the right and the ability to direct and control the activities of VHI in several ways, including through Illumina's 100% ownership of VHI, through instituting programs and measures (such as policies and protocols) at VHI, and through interim instructions via at least Illumina's employees and/or officers who hold leadership roles at VHI. Further, VHI acts on behalf of Illumina, including when VHI performs tests on Illumina's behalf for Illumina's patients, or provides test results to health care providers and/or patients on Illumina's behalf. (*Id.*).

105. In addition or in the alternative, Defendants have also induced infringement, and continue to induce infringement, of one or more of the claims of the '200 Patent under 35 U.S.C. § 271(b). Defendants actively, knowingly, and intentionally induce infringement of the '200

Patent by selling or otherwise supplying the Verifi Tests to third-party laboratories with the knowledge and intent that the third-party laboratories will use the Verifi Tests supplied by Defendants to infringe the '200 Patent. Defendants act with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the Verifi Tests and/or the creation and dissemination of supporting materials, instructions, manuals, guides, and/or technical information related to the Verifi Tests.

106. Defendants specifically intend and are aware that the ordinary and customary use of the Verifi Tests by their customers and partners would infringe the '200 Patent. For example, Defendants sell and provide the Verifi Tests, which when used in their ordinary and customary manner intended and instructed by Defendants, infringe one or more claims of the '200 Patent, including at least claim 1. On information and belief, Defendants further provide product manuals and other instruction materials that cause their customers and partners to operate the Verifi Tests for their ordinary and customary use. (*See, e.g.*, Ex. 9 (https://www.illumina.com/clinical/illumina_clinical_laboratory/verifi-prenatal-tests.html) ("Physicians can order this Illumina service through our network of partner labs.").) Defendants accordingly induce third parties to use Verifi Tests in their ordinary and customary way to infringe the '200 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '200 Patent.

107. In addition or in the alternative, Defendants contribute to the infringement by third parties, such as health care providers or laboratories of one or more of the claims of the '200 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Verifi Tests knowing that those products constitute a material part of the inventions of the '200 Patent, knowing that those products are especially made or

adapted to infringe the ’200 Patent and knowing that those products are not staple article of commerce suitable for substantial non-infringing use.

108. As another example, Defendants infringe at least Claim 1 of the ’200 Patent by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, the VeriSeq Tests and TSO500 Tests. For example, use of the VeriSeq Tests and TSO 500 Tests require a method for reducing template cross-over error introduced during sequencing workflow, the method comprising the steps of:

a. detecting the presence of two or more identifier sequences (such as dual indexes) that are uniquely associated with the nucleic acid analyte of interest (such as a DNA sample), wherein at least a first identifier sequence is incorporated into a 5' portion of the nucleic acid analyte of interest and wherein at least a second identifier sequence is incorporated into a 3' portion of the nucleic acid analyte of interest, and wherein the first and second identifier sequences have four or more nucleotides and are different (Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) (“Each sample in a set of 24, 48, or 96 receives a unique indexed adapter.”); *see also id.* at 10 (Requiring a next generation sequencer that is “[c]ompatible with VeriSeq NIPT Sample Prep dual index adapters”); Ex. 29 at 1212 (Pertile et al.) (“The indexed adapters allowed sample identification and contained sequences that allowed for library capture on the solid surface of a sequencing flow cell for cluster generation and subsequent sequencing. Individual libraries were quantified before pooling.”); Ex. 30 at 35-36 (VeriSeq NIPT Solution v2 Software Product Documentation) (instructing how to demultiplex sequencing data containing i7 and i5 indexes); Ex. 40 at 11 (TruSight Oncology 500 ctDNA Reference Guide) (“In this step, library

fragments are amplified using primers that add index sequences for sample multiplexing. The resulting product contains the complete library of cfDNA fragments flanked by index sequences and adapters for cluster generation."), at 12 ("When sequencing multiple libraries on a single flow cell, assign a different indexing primer to each sample library. Record sample layout orientation and the indexes for each sample library."); Ex. 41 at 46-51 (Illumina Adapter Sequences Data Sheet) (listing dual index adapters to be used with TSO 500 tests).);

b. sequencing the first identifier sequence, the nucleic acid analyte of interest and the second identifier sequence (Ex. 29 (Pertile et al.) ("Sequencing was carried out using a NextSeq 550Dx instrument (Illumina) and the NextSeq 550Dx Reagent Kit v2.5 (Illumina)."); *see also*, Ex. 28 at 3 (VeriSeq NIPT Solution v2 Package Insert) ("The sample libraries are pooled together into 24- or 48- sample pool in adjusted amounts to minimize variation in coverage. Each sample is then sequenced using a next-generation sequencing system."); Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).); and

c. validating the sequence of the nucleic acid analyte of interest by analyzing both identifiers and excluding the sequences of those nucleic acid analytes of interest

containing only one identifier or an incorrect pair of identifiers from sequence analysis of the multiplex sequencing reaction (Ex. 28 at 35 (VeriSeq NIPT Solution v2 Package Insert) ("After sequencing data are collected, they are demultiplexed, converted to a FASTQ format, aligned to a reference genome, and analyzed for aneuploidy detection."), at 3 ("Indexes allow sample identification in subsequent sequencing …Identification of library fragments by index sequence and alignment of the paired end reads to a human reference genome."); Ex. 30 at 35-36 (VeriSeq NIPT Solution v2 Software Product Documentation) (instructing how to demultiplex sequencing data containing i7 and i5 indexes); Ex. 39 at 5 (DRAGEN Analysis Workflows Webpage) ("Sequencing data [for the TSO 500 test] stored in BCL format are demultiplexed through a process that uses the index sequences unique to each sample to assign clusters to the library from which they originated. Each cluster contains two indexes (i7 and i5 sequences, one at each end of the library fragment). The combination of those index sequences are used to demultiplex the pooled libraries. After demultiplexing, this process generates FASTQ files, which contain sequencing reads for each individual sample library and the associated quality scores for each base call, excluding from any clusters that did not pass filter.").).

109. Defendants have infringed, and continue to infringe, one or more claims of the '200 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Accused Products either themselves and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Accused Products.

110. In addition or in the alternative, Defendants have induced infringement, and continue to induce infringement, of one or more of the claims of the '200 Patent under 35 U.S.C. § 271(b). Defendants actively, knowingly, and intentionally induce infringement of the '200 Patent by selling or otherwise supplying the VeriSeq Tests and TSO 500 Tests to third-party laboratories with the knowledge and intent that the third-party laboratories will use the VeriSeq Tests and TSO 500 Tests supplied by Defendants to infringe the '200 Patent. Defendants act with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the VeriSeq Tests and TSO 500 Tests and/or the creation and dissemination of supporting materials, instructions, manuals, guides, and/or technical information related to the VeriSeq Tests and TSO 500 Tests.

111. Defendants specifically intend and are aware that the ordinary and customary use of the VeriSeq Tests and TSO 500 Tests would infringe the '200 Patent. For example, Defendants sell and provide the VeriSeq Tests and TSO 500 Test, which when used in their ordinary and customary manner intended and instructed by Illumina, infringe one or more of the claims of the '200 Patent, including at least claim 1. On information and belief, Defendants further provide product manuals, guides, and other instructional materials that cause their customers and partners to operate the VeriSeq Tests and TSO 500 Tests for their ordinary and customary use. Defendants accordingly induce third parties to use the VeriSeq Tests and TSO 500 Tests in their ordinary and customary way to infringe the '200 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '200 Patent.

112. In addition or in the alternative, Defendants contribute to the infringement by third parties, such as health care providers or laboratories of one or more of the claims of the '200 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or

importing into the United States, the VeriSeq and TSO 500 Tests knowing that those products constitute a material part of the inventions of the ’200 Patent, knowing that those products are especially made or adapted to infringe the ’200 Patent and knowing that those products are not staple article of commerce suitable for substantial non-infringing use.

113. Defendants have had knowledge of and notice of the ’200 Patent and their infringement since at least September 26, 2023.

114. Defendants’ infringement of the ’200 Patent was, and continues to be, willful and deliberate since at least September 26, 2023.

115. Molecular Loop has been and continues to be damaged by Defendants’ infringement of the ’200 patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

116. Defendants’ conduct in infringing the ’200 patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

COUNT 3

(Infringement of the ’730 Patent)

117. Paragraphs 1 through 116 are incorporated by reference as if fully stated herein.

118. The ’730 patent is valid and enforceable.

119. Defendants have infringed, and continue to infringe, one or more claims of the ’730 patent under 35 U.S.C. § 271, either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including at least the TSO 500 Tests.

120. As one example, Defendants infringe at least claim 1 of the '730 patent by using the TSO 500 Tests. For example, use of the TSO 500 Tests require a method for correcting errors or bias introduced during nucleic acid analysis workflow, the method comprising the steps of:

a. obtaining a biological sample (such as DNA or tissue) comprising a plurality of target nucleic acid molecules from more than one locus of origin (Ex. 35 at 2 (TruSight Oncology 500 ctDNA Product Data Sheet) ("Cell-free DNA is extracted from plasma"), at 4 ("TruSight Oncology 500 ctDNA enables comprehensive genomic profiling from just 30 ng of cfDNA, making it an ideal alternative for use when tissue is not readily available or as a complement to tissue analysis.").) The TSO 500 and TSO 500 HT tests require DNA or RNA from tissue samples. (*See, e.g.*, Ex. 36 at 1 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) ("Enabling flexible, scalable comprehensive genomic profiling from FFPE samples."), at 2 ("Minimum recommendation of 2 mm from FFPE tissue samples.").);

b. introducing a set of differentiator tags (such as unique molecular identifiers), wherein members of said set of differentiator tags are associated with members of said plurality (such as DNA fragments), such that one or more of said loci of origin are associated with more than one differentiator tag (Ex. 35 at 1 (TruSight Oncology 500 ctDNA Product Data Sheet) ("Library preparation incorporates unique molecular identifiers (UMIs) that enable ultra-low frequency variant identification."), at 5 ("To enable ultra-low frequency variant identification, library preparation takes advantage of target enrichment with biotinylated probes and streptavidin-coated magnetic beads to enrich for selected DNA-based libraries and

unique molecular identifiers (UMIs) to reduce error rates."), at 6 (showing figure ligating UMI adapters to DNA); *see also*, Ex. 36 at 6 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) ("During library preparation, unique molecular identifiers (UMIs) are added to gDNA or cDNA fragments. These UMIs enable detection of variants at low variant allele frequency (VAF) while simultaneously suppressing errors, providing high analytical specificity."), at 8 ("The addition of UMIs during library preparation coupled with proprietary Illumina informatics reduces sequencing error rates by 10-20 fold."); Ex. 37 at 1 (TruSight Oncology UMI Reagents Products Data Sheet) ("Error correction with unique molecular identifiers (UMIs) for sequencing libraries."), *id.* ("Illumina offers the TruSight Oncology UMI Reagents, which implement UMIs and error correction software to lower the rate of inherent errors in NGS data. The UMI reagents integrate easily with the TruSight Oncology workflow by simply replacing standard Y-shaped adapters with UMI-containing adapters to barcode each individual DNA strand."), at 2 (depicting error correction with UMIs).);

c. amplifying each of the plurality of tagged target nucleic acid molecules to generate amplicons (Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).);

d. sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence (Ex. 38 at 5 (TruSight Oncology 500 ctDNA v2 Product Data Sheet) ("TruSight Oncology 500 ctDNA v2 libraries are sequenced on the NovaSeq 6000 Sequencing System, NovaSeq 6000Dx Instrument (RUO mode), and NovaSeq X Sequencing System at high depth."), at 3 (requiring Illumina NovaSeq sequencers in the specifications for TSO 500 ctDNA); Ex. 36 at 2 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) (requiring NextSeq 550 or NovaSeq 6000 sequencers for TSO 500 and TSO 500 HT respectively).); and

e. correcting for error or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count (Ex. 35 at 4 (TruSight Oncology 500 ctDNA Product Data Sheet) ("DRAGEN TruSight Oncology 500 ctDNA Analysis Software uses accelerated, fully integrated bioinformatics algorithms to ensure optimal assay performance. The software performs sequence alignment, error correction by collapsing the sequence, then variant calling based on the raw data. Duplicated reads and sequencing errors are removed without losing signal for low-frequency variants while yielding high-sensitivity variant calling results."); *see also* Ex. 36 at 7 (TruSight Oncology 500 and 500 High Throughput Product Data Sheet) ("Variant calling for TruSight Oncology 500 and TruSight Oncology 500 High-Throughput is available with DRAGEN secondary analysis either on premise using a local DRAGEN Server or in the cloud using Illumina Connected Analytics (ICA), now with data streaming

and autolaunch capabilities. Both versions take advantage of sophisticated, proprietary algorithms that remove errors, artifacts, and germline variants."); Ex. 37 at 1 (TruSight Oncology UMI Reagents Products Data Sheet) ("Error correction with unique molecular identifiers (UMIs) for sequencing libraries."), at 2 ("After UMI-containing libraries are sequenced, the UMI Error Correction App aligns reads, then collapses the sequences with shared UMIs down to unique reads (Figure 3). This process enables the filtering of false positives, which are excluded from the collapsed reads, reducing the error rate for variant calling."); Ex. 39 at 2 (DRAGEN Analysis Workflows Webpage) (The alignment step [for the TSO 500 ctDNA Test] uses DRAGEN Aligner with UMI collapsing to align DNA sequences in FASTQ files to the hg19_decoy genome. This step combines sets of reads (ie, families) that are grouped together based on genomic locations and UMI tags into representative sequences. This process accurately removes duplicate reads and sequencing errors without losing the signal of very low frequency (<1%) sequence variations."), at 6 ("DNA alignment and error correction involves aligning sequencing reads derived from DNA libraries to a reference genome and correcting errors in the sequencing reads prior to variant calling.…Reads from the same original DNA molecule are tagged with the same UMI during library preparation [of the TSO 500 test]. The UMI allows DRAGEN to compare related reads, remove outlier signals, and collapse multiple reads into a single high-quality sequencing.").).

121. Defendants have infringed, and continue to infringe, one or more claims of the '730 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using

the Accused Products either themselves and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Accused Products.

122. In addition or in the alternative, Defendants have induced infringement, and continue to induce infringement, of one or more of the claims of the '730 Patent under 35 U.S.C. § 271(b). Defendants actively, knowingly, and intentionally induce infringement of the '730 Patent by selling or otherwise supplying the TSO 500 Tests to third-party laboratories with the knowledge and intent that the third-party laboratories will use the TSO 500 Tests supplied by Defendants to infringe the '730 Patent. Defendants act with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the TSO 500 Tests and/or the creation and dissemination of supporting materials, instructions, manuals, guides, and/or technical information related to the TSO 500 Tests.

123. Defendants specifically intend and are aware that the ordinary and customary use of the TSO 500 Tests would infringe the '730 Patent. For example, Defendants sell and provide the TSO 500 Test, which when used in their ordinary and customary manner intended and instructed by Illumina, infringe one or more of the claims of the '730 Patent, including at least claim 1. On information and belief, Defendants further provide product manuals, guides, and other instructional materials that cause their customers and partners to operate the TSO 500 Tests for their ordinary and customary use. Defendants accordingly induce third parties to use the TSO 500 Tests in their ordinary and customary way to infringe the '730 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '730 Patent.

124. In addition or in the alternative, Defendants contribute to the infringement by third parties, such as health care providers or laboratories of one or more of the claims of the '730 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or

importing into the United States, the TSO 500 Tests knowing that those products constitute a material part of the inventions of the '730 Patent, knowing that those products are especially made or adapted to infringe the '730 Patent and knowing that those products are not staple article of commerce suitable for substantial non-infringing use.

125. Defendants have had knowledge of and notice of the '730 Patent and their infringement since at least December 12, 2023.

126. Defendants' infringement of the '730 Patent was, and continues to be, willful and deliberate since at least December 12, 2023.

127. Molecular Loop has been and continues to be damaged by Defendants' infringement of the '730 patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

128. Defendants' conduct in infringing the '730 patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Molecular Loop prays for judgment as follows:

A. That Defendants have infringed each of the Patents-in-Suit;

B. That Defendants' infringement of each of the Patents-in-Suit has been willful;

C. That Molecular Loop be awarded all damages adequate to compensate it for Defendants' past infringement and any continuing or future infringement of the Patents-in-Suit up until the date such judgment is entered, including pre- and post-judgment interest, costs, and disbursements as justified under 35 U.S.C. § 284;

D. That any award of damages be enhanced under 35 U.S.C. § 284 as result of Illumina and VHI's willful infringement;

E. That this case by declared an exceptional case within the meaning of 35 U.S.C. § 285 and that Molecular Loop be awarded the attorney fees, costs, and expenses incurred in connection with this action;

F. That Molecular Loop be awarded either a permanent injunction, or, at least, a compulsory ongoing licensing fee; and

F. That Molecular Loop be awarded such other and further relief at law or equity as this Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff Molecular Loop hereby demands a trial by jury on all issues so triable.

Dated: June 10, 2024

Respectfully submitted,

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